Letters to the Editor . . .

San Francisco

Editor, CALIFORNIA MEDICINE

Dear Sir:

In a recent contribution, Rothman[2] estimated the total number of new cases of rheumatic fever occurring in residents of Los Angeles under 19 years of age to be 44 annually. This conclusion was based upon the application of a formula derived from the observations of Coombs[1] upon 218 rheumatic children followed in Bristol, England, between 1903 and 1919. It was found that 11.2 per cent (23 patients) died within five years after the onset of rheumatic infection.

In Rothman's series, 25 deaths due to rheumatic fever occurred amongst an unknown total number of cases, and he concluded that the number of new cases in Los Angeles in any year is "about 44" in the age group below 19.

Coombs and Rothman were dealing with approximately the same number of deaths during a five-year period (23 in Coombs' series, and 25 in Rothman's), yet Rothman estimated only about 20 per cent (44) of the number of cases which Coombs was actually following (218). The basis for this inconsistency is Rothman's use of a formula as follows:

Let x = the number of new cases in one year.

Let 11.2 per cent of x = the number of deaths in a five-year period (1939-43), among cases new in one year (1939 or any one year).

Since there were 25 deaths in five years, take five deaths for any one year; then 11.2 per cent of $x = 5$, and $x = 44$ new cases per year.

This is the fallacy: the year of onset of the disease in Rothman's cases, if known, is not taken into account, and there is no basis for assuming that 11.2 per cent of $x = 5$, since there is no information that there were five deaths in the five-year period 1939-43 among *cases new in 1939*. Hence by the use of an invalid formula, a meaningless estimate of the incidence of rheumatic fever in Los Angeles is obtained.

The difficulties in determining the incidence of rheumatic fever in any area are great. The disease, moreover, is variable from patient to patient, from place to place and from time to time. Even if Coombs' studies, made from 30 to 46 years ago, were properly applied to the Los Angeles area at this time, it is doubtful if accurate or important information would be derived. A simpler method of obtaining information concerning the incidence of rheumatic fever in Los Angeles and in California is to refer to the data reported currently by local physicians. These data, although subject to the usual errors of reporting and classification, indicate the local problem to be quite appreciable, as follows:

MORBIDITY FROM RHEUMATIC FEVER—LOS ANGELES COUNTY AND CALIFORNIA[3]
1948

	L. A. County	*California*
Number of children under 21 with rheumatic fever or rheumatic heart disease on the California Crippled Children Register as of Dec. 31, 1948	1,252	4,737
Number of children under 21 with rheumatic fever or rheumatic heart disease first reported to the Crippled Children Register during 1948	341	946

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Immunity Potential of Diabetics

In 1942, Cannon[2] and his associates of the department of pathology, University of Chicago, introduced the new concept of "immunity potential" into physiologic theory. This was measured in terms of the titer of specific antibodies produced by an individual following injection of an arbitrary standard dose of specific antigen. Evidence was cited suggesting that antibodies are manufactured largely from ingested proteins and protein-reserves.[3] They found that rats whose serum proteins had been reduced one-half by prolonged low protein diets produce less than one-hundredth the hemolysin and agglutinin titers produced by adequately nourished control rats.[1]

Clinical applications of Cannon's theory are reported by Wohl[4] and his associates of Philadelphia General Hospital. For these applications they selected 64 diabetic patients and 11 non-diabetic controls. Most of the individuals were given an injection of a standard dose of typhoid H antigen on the sixth, tenth and twentieth days, with periodic determinations of the resulting typhoid H agglutinin titer. Titers as high as 1:5120 and as low as 1:40 were recorded.

Plotting these titers against the fasting venous blood sugar levels showed that antibody production is independent of diabetic severity as determined by blood sugar levels. A positive correlation, however, was noted between antibody production and serum proteins. Sixteen diabetic patients with serum albumin levels below 4 grams per 100 cc. produced anti-

serums with an average agglutinin titer of but 1:800. An average titer of 1:2900 was produced by control normoproteinemic diabetics.

Nineteen hypoproteinemic patients were given protein supplements in the form of lactalbumin hydrolysate or casein concentrate. This was given in isocaloric diets in sufficient quantities to double the daily protein intake. The serum albumin of these patients rose from an average of 3.11 grams to 3.87 grams per 100 cc. by the end of 27 days. Their average agglutinin production was doubled by the end of this period. The extra proteins did not appear to increase the severity of the diabetes, as determined by the blood sugar levels.

A similar poor antibody response was demonstrated[5] with hypoproteinemic non-diabetics. Wohl observed a suggested correlation between hypoproteinemia and the tendency of diabetics to develop such complications as gangrene and osteomyelitis.

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Ineffective Booster Vaccines

In 1924, Wilkins and Wells[5] reported the successful control of an outbreak of dysentery in a children's institution by the use of a vaccine prepared from a Shigella culture isolated in the institution. Similar successes were afterwards reported by Paddle,[4] Felsen,[2] and Klimentova.[3]These successes have led to numerous investigations of specific antibody production in human volunteers following injections of killed dysentery cultures.

For example, Cooper[1] and his associates of the department of pediatrics, University of Cincinnati, found that volunteers given repeated injections with monovalent dysentery vaccines produce both specifice agglutinating and mouse protective antibodies. After vaccination with certain Shigella cultures the protective antibodies persist for only six to ten weeks. With other monovalent dysentery vaccines they persisted as long as 24 to 52 weeks. With a pentivalent vaccine made from a mixture of equal amounts of five Shigella cultures a 640-fold increase in mouse protection titer was noted one week after the third dose. The titer gradually fell to the 320-fold level by the end of six months, and to 80-fold level by the end of one year. The titer was not the same for all five components of the pentivalent vaccine.

Less encouraging results were obtained with booster vaccines. Two booster injections of Sh. flexneri III, given 24 weeks after primary homologous vaccination, did not stimulate increases in the mouse protective titer of the serums of ten children tested with this vaccine. This was attributed to the fact that statistically significant levels of mouse protective antibodies formed as a result of the first vaccination were still present at the time of the first booster injection. This interpretation was confirmed by the fact that three booster injections of Sh. flexneri VI, given 54 weeks after primary vaccination, when the initial protective titer of the serums had fallen to zero, did stimulate statistically significant increases in mouse protective titer, which persisted for at least six weeks.

Confirmatory results were also obtained with a pentivalent vaccine. Three booster injections of the mixed vaccine given 78 weeks after primary homologous vaccination stimulated significant increases in the mouse protective titer for the four components of the vaccine against which the initial mouse protective titer had decreased to practically zero. No significant increase was noted in the mouse protective titer against the fifth component, against which there was still a significant residual antibody titer at the time of the first booster injection.

If a similar dependence of booster effects upon a negative residual antibody titer is demonstrated with other prophylactic vaccines, modifications of conventional clinical methods may follow. However, no deleterious effects following the use of ineffective dysentery booster vaccines have thus far been reported.

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